nucleic acid and do not hybridize to each other, and the signal sequence probe hybridizes to the bridge probe and does not hybridize to the target nucleic acid and the capture sequence probe;

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b) adding a blocker probe to the hybridization reaction, wherein said blocker probe hybridizes to excess non-hybridized capture sequence probes;

c) capturing the hybrid to form a bound hybrid; and

d) detecting the bound hybrid.

51. (amended)The method according to claim 50, wherein the signal sequence probe comprises a DNA-RNA duplex and a single stranded nucleic acid which hybridizes to the bridge probe.

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55. (amended)The method according to claim 54, wherein the signal sequence probe comprises a single stranded poly(dT) DNA sequence which hybridizes to the poly(A) tail of the bridge probe, and a DNA-RNA duplex formed between the poly(dT) sequences in the signal sequence probe and a nucleic acid molecule having poly(A) sequences.

REMARKS

Applicants respectfully request favorable reconsideration in view of the herewith presented amendments and remarks.

Claims 1-46 and 48-55 are pending in this application.

35 U.S.C. §112

Claims 1, 2, 19, 21-22, 40, 42, 50-51, 55 and dependent claims 3, 4-18, 20, 23-39, 41, 43-46, 49, 52-54 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. In particular, the Examiner objects to the recitation of "capable of hybridizing" as indefinite because capability is a latent characteristic and the claims do not set forth the criteria by which to determine capability. Further, the Examiner objects to the recitation because it is not clear whether the recited set of probes

have the potential to hybridize or do in fact hybridize the recited target nucleic acid which is to be detected. Applicants respectfully disagree with this rejection.

However, in order to expedite prosecution of the instant application, applicants have amended claims 1-2, 19, 21-22, 40, 42, 50-51, and 55 in order to address the Examiner's concerns regarding this issue. Reconsideration and withdrawal of this §112 rejection is respectfully requested.

35 U.S.C. §103

Claims 1-6, 10-12, 15-27, 30-38, 40-46, and 48-55 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Engelhardt et. al. (USPN: 6,221,581) and in view of Pandian et al. (USPN: 5,627,030). Applicants respectfully disagree with this rejection.

As an initial matter, the Examiner appears to have ignored the limitations of the claims by rejecting all of the above-listed claims without considering the distinguishing features of the different claims. In particular, claims 1-6, 10-12, 15-21, 32, 37-38, and 48-55 are directed to methods using blocker probes and bridge probes. Claims 22-27, 30-31, and 33-36 are directed to methods using a detectably labeled RNA:DNA hybrid antibody for the detection of a target nucleic acid. Claims 40-46 contain a specific recitation to a method of detecting a target nucleic acid sequence, where a signal sequence probe when hybridized with a target nucleic acid, forms a DNA:RNA hybrid complex. The limitations in each claim form the basis of protectable subject matter and must form the basis of rejections on patentability grounds. The Examiner appears to have lumped all of the above-listed claims into a single group without considering the specific limitations in each.

In general, the Engelhardt reference describes a method of detecting a target nucleic acid. The Examiner has combined the Engelhardt reference with the Pandian reference, the latter of which describes a method for detecting a target nucleic acid – probe complex. The Examiner specifically utilizes the Pandian reference with the Engelhardt reference to reject claims directed to blocker probes and bridge probes (i.e., claims 1-6, 10-

12, 15-21, 32, 37-38, and 48-55). However, these references do not teach or suggest the claimed invention, either alone or in combination with each other.

Regarding the rejection to claims 1-6, 10-12, 15-21, 32, 37-38, and 48-55, which are directed to using blocker probes and bridge probes, the Examiner alleges that the Engelhardt reference describes a method of detecting a target nucleic acid. Applicants assert that the Engelhardt reference does not teach or suggest the method of detecting a target nucleic acid as claimed. In fact, the Examiner readily admits that the primary reference (i.e. Engelhardt et al.) does not teach or suggest the use of blocker probes and bridge probes as claimed. The Examiner then combines Engelhardt with a second reference, Pandian et al. The Examiner alleges that Pandian describes an amplification probe which, according to the Examiner, functions as both blocker and bridge probes. Applicants respectfully disagree with this rejection.

In particular, Applicants respectfully disagree with the Examiner's characterization of the Pandian reference. The Examiner essentially equates the amplification probes of the Pandian reference to blocker probes of the instant claims (i.e., claims 1-6, 10-12, 15-21, 32, 37-38, and 48-55) when referring to column 5, lines 48-56. However, the amplification probes of Pandian do not function as blocker probes, nor do these probes bind to the "excess non-hybridized CSPs" as do the claimed blocker probes.

In the Pandian reference, the amplification probes are described to hybridize to "at least one labelling nucleic acid sequence, conjugated to a chemical label (the labelling probe)" (col. 5, lines 31-33) used for signal detection. At its other end, the Pandian "amplification probe" hybridizes to the "primary probe" (column 5, lines 26-30). As a result, the amplification probe forms a complex which does not function as do the claimed blocker probes. The Examiner's attention is respectfully drawn to the Pandian reference, column 5, lines 26-32, column 6, lines 45-55, and column 7, lines 16-21. The amplification probe complex described in Pandian cannot distinguish between a target nucleic acid-probe complex and a primary probe-amplification probe complex as can the claimed blocker probes, because the amplification probe is designed to hybridize to the primary probe and NOT the "excess non-hybridized CSP", as is claimed for the instant blocker probes. In fact, the claimed blocker probes contain sequences identical to regions of the target. The Examiner's reliance on Pandian, column 5, lines 48-56 is misplaced in that this section does

not teach or suggest the use of probes which hybridize to excess non-hybridized capture sequence probes or probes of any kind. Therefore, Pandian does not teach or suggest the use of blocker probes as claimed. Reconsideration and withdrawal of the §103 rejection with response to claims 1-6, 10-12, 15-21, 32, 37-38, and 48-55 is respectfully requested.

As relates to claims 50-55 which are directed to the use of bridge probes, the Examiner alleges that the Pandian reference describes that "the hybrid complex can be hybridized to an amplification probe (bridge probes) with repeat sequences" (Paper No. 12, pg. 4, lines 18-19). However, the amplification probe of Pandian hybridizes to the primary probe, and NOT the target sequence, as does the claimed bridge probe. The amplification probe of the Pandian reference does not hybridize to the target nucleic acid. Unlike the Pandian reference, the claimed bridge probe directly hybridizes to the target nucleic acid. The Pandian reference does not teach or suggest the detection of target nucleic acid – probe complexes using bridge probes as disclosed in claims 50-55. The skilled artisan would have no motivation to combine or modify the teachings of Engelhardt et al. and Pandian et al. to correspond to the claimed invention. Applicants respectfully request reconsideration and withdrawal of this §103 rejection.

Further, Applicants respectfully disagree with the Examiner's assertion that an "amplification probe...with poly (A) tail (column 6, lines 4-13)" (Paper No. 12, pg. 4, lines 17-18) would make the claimed bridge probes obvious to one skilled in the art. The Examiner has characterized the Pandian reference in column 6, lines 4-13 as describing that "amplification probes can be with poly(A) tail". Pandian does not state this. See column 6, line 5. If the Examiner intended the amplification probe with a poly(A) tail of the Pandian reference to be equivalent to the claimed bridge probe having a poly(A) tail, the significant difference between the two probes is that the amplification probe does not hybridize to the target nucleic acid, as does the claimed bridge probe. In Pandian, the primary probe hybridizes to form a double stranded hybrid with the target.

If the Examiner intended the primary probe to be equivalent to the claimed bridge probe, this too is distinguishable. The double stranded nucleic acid complex of the Pandian reference is used for immobilization and detecting the complex. In contrast, the bridge probe of the claimed invention, is NOT involved in immobilization, but rather

facilitates detection of the nucleic acid complex. In particular, the claimed invention utilizes a bridge probe such that the bridge probe hybridizes to the target nucleic acid and an unlabeled SSP. The poly(A) tail portion of the bridge probe – SSP hybrid forms a double stranded molecule for antibody detection. The claimed immobilization function of the nucleic acid probes is carried out with a separate probe, i.e. CSP. This feature is not taught or suggested in the Pandian or Engelhardt references. Therefore, the Pandian probes do not function as bridge probes as claimed, and the Engelhardt reference does not remedy this defect in the Pandian reference. Thus, Engelhardt in view of Pandian does not teach or suggest the invention in claims 54 and 55. Reconsideration and withdrawal is respectfully requested.

Claims 22-27, 30-31, and 33-36 that are directed to methods of using a detectably labeled RNA:DNA hybrid antibody for the detection of a target nucleic acid have been rejected. The Examiner's position is that one skilled in the art would be able to use a double stranded nucleic acid hybrid antibody for detecting a target nucleic acid as claimed in claims 22-27, 30-31, and 33-36 based upon a teaching in Engelhardt (column 8, lines 37-65). Applicants respectfully disagree with the Examiner's rejection.

In particular, the Examiner alleges that the Engelhardt reference describes a method of detecting a target nucleic acid – probe hybrid complex which utilizes an antibody to double stranded genetic material (column 8, lines 37-54). The Examiner does not rely on Pandian for any particular teaching. In fact, the Pandian reference adds nothing to the Engelhardt reference so that the skilled artisan could reach the specific invention of claims 22-27, 30-31, and 33-36. Applicants respectfully disagree with the Examiner's description of the Engelhardt reference.

The embodiment of the Engelhardt reference cited by the Examiner (column 8, lines 37-65) utilizes only "one polynucleotide probe and, rather than utilizing the second polynucleotide probe, an antibody to double stranded genetic material" (column 8, lines 37-40) is utilized. As a result, Engelhardt teaches the skilled artisan to use ONE nucleic acid probe in combination with a double stranded nucleic acid antibody. In fact, the Engelhardt reference uses a single nucleic acid probe and an antibody that immobilizes the double stranded nucleic acid that forms when the target is hybridized to the one single stranded nucleic acid probe. It also states in the Engelhardt reference that it is <u>essential</u> for either or

both the single stranded nucleic acid probe or the antibody be labeled with a particle. (See Engelhardt, column 8, lines 46-50). This is not the case in the instant claims. Claims 22-27, 30-31, and 33-36 require two separate probes and detection using a DNA-RNA antibody. Therefore, this reference clearly teaches away from using two separate polynucleotide probes and an antibody directed against double stranded nucleic acids as claimed in the instant invention. In fact, the Engelhardt et al. reference provides no motivation for modification in order to fit the claimed invention. Therefore, the skilled artisan would not be motivated to use two separate probes and an antibody in view of the Engelhardt and Pandian references. Applicants respectfully request reconsideration and withdrawal of this §103 rejection.

Regarding claims 40-46 which are directed to a method of detecting a target nucleic acid sequence, where a signal sequence probe, when hybridized with a target nucleic acid, forms a DNA-RNA hybrid complex, have been rejected. Applicants respectfully direct the Examiner's attention to the Engelhardt reference (column 9, lines 29-41) where a double stranded DNA or RNA complex is used for immobilization to a matrix. In contrast, the claimed invention uses a DNA-RNA hybrid complex for detection. The Engelhardt reference teaches the use of double stranded nucleic acid hybrids for capturing the target complex to a matrix, and not for detection of the target nucleic acid – probe hybrid complex as claimed. As discussed above, Engelhardt only describes detecting DNA-RNA hybrids when a single nucleic acid probe is used. Further, the Engelhardt reference provides no motivation for modification in order to fit the claimed invention. Finally, the Pandian reference adds nothing to reach the specific invention of claims 40-46. Thus, reconsideration and withdrawal of this §103 rejection is respectfully requested regarding claims 40-46.

As relates to claims 49 and 52, the Examiner rejects these claims which are directed to a M13 DNA-M13 RNA duplex as obvious over the Engelhardt and Pandian references. Applicants respectfully disagree.

The Engelhardt and Pandian references either alone or in combination do not teach or suggest the present invention as claimed. Although the skilled artisan may wish to achieve a highly sensitive and rapid means of hybridization for the detection of a target nucleic acid, the combination of the Engelhardt and Pandian references do not teach or suggest the method of detecting target nucleic acids as disclosed in claims 1-6, 10-12, 15-27,

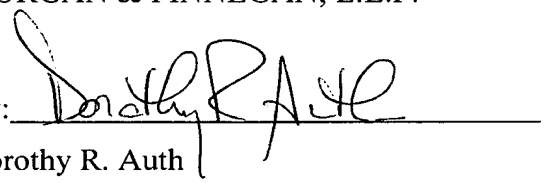
30-38, 40-46, and 48-55. Since the methods of Engelhardt and Pandian do not teach or suggest the instant claims, these references also do not teach or suggest detecting a more complex target such as the M13 phage of claims 49 and 52. Neither reference suggests or motivates one skilled in the art to combine references nor provides basis for modification in order to correspond with the claimed invention. Therefore, Applicants respectfully request reconsideration and withdrawal of this §103 rejection with respect to claims 49 and 52.

Allowance of the pending claims is respectfully requested. Early and favorable action by the Examiner is earnestly solicited.

The Commissioner is hereby authorized to charge any additional fees which may be required for the timely consideration of this amendment under 37 C.F.R. §§ 1.16 and 1.17, or credit any overpayment to Deposit Account No. 13-4500, Order No. 2629-4017.

Respectfully submitted,
MORGAN & FINNEGAN, L.L.P.

Dated: January 9, 2002

By: 
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

As required by 37 C.F.R. 1.121, a marked up version of the replacement claims is as follows:

IN THE CLAIMS

Please amend the claims as follows:

1. (amended)A method of detecting a target nucleic acid comprising:

a) hybridizing a single-stranded target nucleic acid to a capture sequence probe and a signal sequence probe to form double-stranded hybrids between said probes and the target nucleic acid, wherein the capture sequence probe and the signal sequence probe hybridize [are capable of hybridizing] to non-overlapping regions within the target nucleic acid and do not hybridize [not being capable of hybridizing] to each other;

b) adding a blocker probe to the hybridization reaction, wherein said blocker probe hybridizes to excess non-hybridized capture sequence probes;

c) capturing the hybrid to form a bound hybrid; and

d) detecting the bound hybrid.

2. (amended)A method of detecting a target nucleic acid comprising:

a) hybridizing a single-stranded target nucleic acid to an immobilized capture sequence probe and a signal sequence probe to form double-stranded hybrids between said probes and the target nucleic acid, wherein the capture sequence probe and the signal sequence probe hybridize [are capable of hybridizing] to non-overlapping regions within the target nucleic acid and do not hybridize [not being capable of hybridizing] to each other;

b) adding a blocker probe to the hybridization reaction, wherein said blocker probe hybridizes to excess non-hybridized capture sequence probes;

c) detecting the bound hybrid.

19. (amended)The method of claim 1 or 2, wherein the bound hybrid is detected using an antibody which recognizes [capable of recognizing] a hybrid.

21. (amended)The method of claim 20, wherein the antibody which recognizes [capable of recognizing] a DNA-RNA hybrid is labelled with alkaline-phosphatase.

22. (amended)A method of detecting a target nucleic acid comprising:

a) hybridizing a single-stranded target nucleic acid to a capture sequence probe and a signal sequence probe, wherein the capture sequence probe and the signal sequence probe hybridizes [are capable of hybridizing] to non-overlapping regions within the target nucleic acid and do not hybridize [not being capable of hybridizing] to each other, wherein said hybridization forms an RNA-DNA hybrid between said signal sequence probe and the target nucleic acid; and

b) detecting the RNA-DNA hybrid by binding an antibody which recognizes [capable of recognizing] the RNA-DNA hybrid to said hybrid, wherein said antibody is detectably labelled.

40. (amended)A method of detecting a target nucleic acid comprising:

a) hybridizing a single stranded target nucleic acid to a capture sequence probe and a signal sequence probe, wherein the capture sequence probe and the signal sequence probe hybridize [are capable of hybridizing] to non-overlapping regions within the target nucleic acid and do not hybridize [not being capable of hybridizing] to each other, wherein the signal sequence probe comprises a DNA-RNA hybrid region, wherein said hybridization forms a complex; and

b) detecting said complex.

42. (amended)The method of claim 40 wherein said complex is detected by binding an antibody which recognizes [capable of recognizing] the DNA-RNA hybrid region to said region, wherein the antibody is detectably labelled.

50. (amended)A method of detecting a target nucleic acid comprising:

a) hybridizing a single-stranded target nucleic acid to a capture sequence probe, a bridge probe and a signal sequence probe to form double-stranded hybrids between said capture sequence and bridge probes and the target nucleic acid, wherein the capture sequence probe and the bridge probe hybridize [are capable of hybridizing] to non-overlapping regions within the target nucleic acid and do not hybridize [not being capable of hybridizing] to each other, and the signal sequence probe hybridizes [is capable of hybridizing] to the bridge probe and does not hybridize [not being capable of hybridizing] to the target nucleic acid and the capture sequence probe;

b) adding a blocker probe to the hybridization reaction, wherein said blocker probe hybridizes to excess non-hybridized capture sequence probes;

c) capturing the hybrid to form a bound hybrid; and

d) detecting the bound hybrid.

51. (amended)The method according to claim 50, wherein the signal sequence probe comprises a DNA-RNA duplex and a single stranded nucleic acid which hybridizes [is capable of hybridizing] to the bridge probe.

55. (amended)The method according to claim 54, wherein the signal sequence probe comprises a single stranded poly(dT) DNA sequence which hybridizes [is capable of hybridizing] to the poly(A) tail of the bridge probe, and a DNA-RNA duplex formed between the poly(dT) sequences in the signal sequence probe and a nucleic acid molecule having poly(A) sequences.